DOCKET NO: UPAP0025-100 (K1763)
PATENT APPLICATION

Serial No.: 09/719,067
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REMARKS

Status of the Claims

Claims 1-2 and 5-34 are pending.

Claims 1-2 and 5-34 were rejected in the Office Action of June 20, 2005.

By way of this amendment, claims 1, 11, 26, 31 and 33 have been canceled, claims 2, 5, 9, 13, 18, 19, 23-25, 29, 30, 32 and 34 have been amended and new claims 35-39 have been added.

Upon entry of this amendment, claims 2, 5-10, 12-25, 27-30, 32 and 34-39 will be pending.

Summary of the Invention

Claims 2 and 32 have been amended to be dependent on claim 5.

Claim 34 has been amended to be dependent on claim 9.

Claims 5, 9, 18, 19, 23-25 and 29 have been amended to be delete references to macrophage-derived lineage and to include reference to DNA molecules being plasmids.

Claims 5 and 13 have been amended to delete reference to CD156 promoter.

Claim 25 has been amended to include steps of identifying a site proximal to a lymph node having cells to be eliminated.

Claim 30 has been amended to list specific macrophage-specific promoters.

New claims 35 and 37-39 are dependent on claims 5, 9, 18 and 18 respectively and list specific macrophage-specific promoters.

New claim 36 is dependent on claim 9 and refers to a protein that comprises a signal sequence.

Support for the amendments is found throughout the specification and claims as originally filed. No new matter has been added.

Rejection under 35 U.S.C. § 112, first paragraph – Written Description

Claims 1-2, 6-11, 14-16, 18-24, and 29-30 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art, at the time the application was filed, had possession of the claimed invention. The Office alleges that the specification contains only "limited information" and "is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any macrophage-specific promoter, even those found in human genes, at the time the application was filed." (Office Action, page 6). Applicants respectfully disagree.

Claims 2 and 6-8 satisfy the written description requirement. As an initial matter, Applicants respectfully point out that the Examiner did not reject claim 5 as failing to comply with the written description requirement, but the Examiner still rejected claims 6-8 even though they depend upon claim 5 (*see* Applicants Amendment dated 2/15/05). Claim 5 sets forth specific macrophage specific promoters. Accordingly, Applicants respectfully assert that claims 6-8 satisfy the written description requirement. Moreover, claim 2 has been amended to be dependent upon claim 5. Applicants respectfully assert that as amended, claim 2 satisfies the written description requirement.

With regard to the rejection as applied to claims 1, 9-11, 14-16, 18-24, and 29-30, Applicants respectfully urge that the claims satisfy the written description requirement because the macrophage specific promoters claimed in the pending claims is only claiming what is already known to one of skill in the art.

Indeed, the present invention is not dissimilar to that in a recent case in which the Court of Appeals for the Federal Circuit ("Federal Circuit") overturned rejections for lack of written description. See *Capon v. Eshhar*, 418 F.3d 1349, 1355 (Fed. Cir., 2005). In *Capon*,, the claims recited chimeric DNAs (or genes) comprising DNA encoding , for example, a single chain Fv domain of a specific antibody and the transmembrane and cytoplasmic domain of an endogenous protein. *Id.* at 1352. The Board had rejected such

claims for lack of written description, arguing that novel genetic material was being described in terms of the functional characteristics of the protein encoded. *Id.* at 1355. The Board, relying upon much of the same precedent relied upon by the Office in rejecting Applicants' claims, was requiring the complete sequence of at least on chimeric gene. *Id.*

In response, the parties argued, *inter alia*, that the chimeric genes are produced by selecting and combining known DNA segments, using known procedures. *Id.* Notably, the Board did not dispute that persons in the field could determine the structure or formula from the known structure of formula of the components. *Id.* The Federal Circuit observed that none of the cases relied upon by the Board required a re-description of what was already known. *Id.* at 1357-1358. The court stated,

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. . . .When the prior art includes the [allegedly lacking] information, precedent does not set a per se rule that the information must be determined afresh.

Id. In the present case, as in *Capon,* the individual components were known. Here, macrophage specific promoters are known to one of ordinary skill in the art just as the sequence of proteins used in the invention of *Capon* were known at the time the application was filed. Thus, the Applicants are not required to describe what is already known in the art (*e.g.* macrophage specific promoters) because the invention is not the promoters themselves but rather a method of using the promoter as described in the pending claims.

Applicants clearly had possession of the invention at the time the Application was filed because Applicants disclosed numerous examples of macrophage specific promoters and one of skill in the art would understand that the present invention includes those promoters as well as any other promoter that is macrophage specific. The Office has failed to give provide adequate evidence to demonstrate that the claims fail to satisfy the written description requirement. On the contrary, the Office's argument that Applicants

have failed to satisfy the written description requirement actually support the fact that the specification does in fact comply with the written description requirement.

As discussed above, the Office admits that the all the macrophage specific promoters will have the same function. This function is what defines whether or not a promoter from a gene is covered by the claim. For the Office to say that "functional characteristics do not and cannot differentiate one species from other species" would render the guidelines for written description meaningless. The MPEP states:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

(MPEP § 2163). Applicants have shown that the invention is complete by disclosing the function of the promoter and then also providing five examples of promoters that are macrophage specific. Applicants ***are not*** required to supply every macrophage specific promoter that is either known or available in the art, rather Applicant is only required to disclose a representative number of species. The MPEP states

> "representative number of species" means that the species which are adequately described are representative of the entire genus.

(MPEP § 2163). The species described in the present application are adequate to describe the genus. One of ordinary skill in the art would know and understand that Applicants had possession of the entire genus of macrophage specific promoters for the methods described in the pending claims. One of skill in the art would understand that the promoter would comprise a nucleotide sequence and be macrophage specific. As discussed in previous responses and declarations one of ordinary skill in the art would be able to determine if a promoter is macrophage specific without undue experimentation.

Once again, the Office dismisses the relevance of the declaration submitted by Dr. Weiner, which states:

> One of ordinary skill in the art would be able to determine whether a promoter is macrophage specific without undue experimentation by using routine, well known techniques.

The Office states that Dr. Weiner's declaration is "an opinion, because it is not supported by evidence or other scientific reasoning to demonstrate possession." (Office Action, page 7). Applicants respectfully disagree. It is well settled that the question of whether a specification provides an adequate written description of the subject matter of the claims is an issue of fact. The Office was in error when he stated that the Weiner declaration, which attempted to shed light on whether the specification adequately described the claimed subject matter, provided evidence. The Office has not accepted the Weiner declaration as offering factual evidence on the adequate written description issue. In fact, the Weiner declaration provides a clear factual statement. The declaration must be read as offering factual evidence in an attempt to explain whether one of ordinary skill in the art would have understood that applicants were in possession of the claimed invention at the time the application was filed. The declaration demonstrates that one of ordinary skill in the art would be able to determine if a promoter is macrophage specific, which must be accepted as fact by the Office, ***unless the Office has evidence to rebut the statement in the declaration.*** The Office has failed to provide ***any*** evidence to rebut Dr. Weiner's previous declaration. Accordingly, one of skill in the art would know that a macrophage promoter would have a nucleotide sequence (structure) and be macrophage specific (function). These two elements can be used to satisfy the written description requirement. Applicants are not required to provide a core structure beyond a nucleotide sequence nor are Applicants required to provide a consensus sequence of what makes a promoter macrophage specific as the Office alleges. Rather, Applicants are only required to convey possession of the invention to one of ordinary skill in the art by showing that one of skill in the art would understand that the Applicants had possession at the time the application was filed. Clearly, Applicants had possession because a representative number of species are described and one of skill in the art would be able to determine what species of promoters are included in the genus and which are not without an undue burden. Applicants' disclosure demonstrates possession of the claimed invention.

Furthermore, one of skill in the art would ***recognize*** that Applicants were in possession of the necessary "common attributes or features" of the genus. The "common attributes or features" of members of the genus are that the promoters are macrophage specific and they come from a human gene. These features are unambiguous and is discussed in the specification (see, for example, p. 11, lines 16-18).

The Office is respectfully reminded that, "[d]escription of a representative number of species ***does not require*** the description to be of such specificity that it would provide individual support for each species that the genus embraces." (M.P.E.P. § 2163, emphasis added). Therefore, in addition to the species described in the present Application, Applicants were in possession of the genus that includes promoters that are macrophage specific in a human.

The courts have stated, for example,

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention. (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement...by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention."

(*University of California v. Eli Lilly and Co* (CA FC) 43 USPQ2d 1398, @1404, citations omitted). The specification describes the invention specifically and with "sufficient detail" that one skilled in the art would conclude that Applicants were in possession of the invention. Accordingly, Applicants have demonstrated possession of the invention and satisfied the requirements for Written Description. Applicants have described what is meant by a macrophage specific promoter (regardless of its origin) and one of skill in the art would, therefore, know that Applicants were in possession of the claimed invention when the application was filed.

Furthermore, as discussed previously, the present invention is not claiming "macrophage specific promoters," *per se*. Rather the pending claims that include the

term "macrophage specific promoter" only refer to one element of the nucleotide sequence that is being ***used*** in the claimed method.

In view of the foregoing, Applicants respectfully request that the rejection alleging that the claims fail to satisfy the Written Description requirement be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The enablement rejections as set forth in the Official Action are provided in two parts. In the first, claims 1-2, 5-11, 13-17, 29, and 32-34 stand rejected under 35 U.S.C. § 112, first paragraph, because while enabling specific embodiments, it is asserted that the specification the claims does not enable the claimed invention for

> any macrophage-derived lineage, any type of DNA molecule, any macrophage specific promoter derived from a human gene, a catalase promoter, a p73 promoter, the delivery of proteins to the lymphnodes where the protein is not linked to a secretion signal, or the delivery of proteins to a lymphnode not proximal to the site of injection.

(Official Action, page 10). In the second part, claims 18-28 and 30-31 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. This part includes an analysis under the factors set forth in *In re Wands*. Applicants respectfully urge that the claims are enabled.

With respect to the rejection as applied to claims 1-2, 5-11, 13-17, 29, and 32-34, Applicants urge that all claims which remain pending no longer refer to "cells of macrophage-derived lineage." In addition all claims which remain pending upon entry of the amendment set forth that the DNA molecule is a plasmid. In each claim that listed "a catalase promoter" and "a p73 promoter" such references have been deleted.

Claims 9, 10 and 13-16, which refer to the delivery of proteins to a lymphnode specifically refer to methods for delivering such proteins to a lymphnode proximal to the site of injection.

Claims 1, 9, 10 and 14-16 continue to refer to "macrophage specific promoters." Applicants respectfully urge that such subject matter is enabled. One skilled in the art would expect that the invention would function with any other macrophage specific promoter as it does with a CD156 promoter, a M-CSFR promoter or an FcγRI promoter. There is no reasoning or evidence provided in the rejection to support doubting that macrophage specific promoters other than those set forth in the specification would work.

Likewise, claims 9, 10 and 13-16 refer to the delivery of proteins to the lymphnodes where the protein is not limited to proteins linked to a secretion signal. Applicants respectfully urge that it is not required that the proteins include a signal sequence in order for them to be produced by the macrophage and released to the lymph node. There is no reasoning or evidence provided in the rejection to support doubting that proteins could be delivered to the lymphnodes if the proteins is not linked to a secretion signal. would work, or the delivery of proteins to a lymphnode not proximal to the site of injection.

Applicants respectfully assert that the claims as pending are enabled and the that rejection of claims 1-2, 5-11, 13-17, 29, and 32-34 under 35 U.S.C. § 112, first paragraph, as not complying with the enablement requirement should be withdrawn.

As noted above, the second rejection under 35 U.S.C. § 112, first paragraph, asserted that part, claims 18-28 and 30-31 contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. This part includes an analysis under the factors set forth in *In re Wands*. Applicants respectfully urge that the claims are enabled.

In discussing the nature of the invention, the Office alleges that claims are in the field of gene therapy and the field of gene therapy is not enabled (Office Action, page 12). Initially, Applicants point out that claims 18-22 refer to methods of inducing immune responses. It is beyond reasonable debate to characterize claims 18-22 as gene therapy. The induction of immune responses is well established and not considered gene therapy as discussed in the cited references.

Applicants respectfully assert that the Office has misjudged the claims generally. Pending claims are directed towards the delivery of a protein to a macrophage cells or the delivery of a protein to a lymphnode do not share the problems highlighted in the cited art. The Office alleges that the Deonarian reference suggests targeting to desired tissues *in vivo* continues to be a difficulty. (Office Action, page 12). The Office alleges

> One of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant populations of cells and express it at adequate levels for a long enough period of time

(Office Action, page 12). However, the allegation of the Deonarian reference is not relevant to the pending claims. Even if the Deonarian reference is correct, which it may or may not be, the present invention is not hampered by the limitations of other gene therapy techniques in that sustained expression is not necessary for the pending claims to be enabled. Data on the record show that DNA molecules delivered according to the claimed invention are taken up by macrophage cells. The specification provides ***specific working embodiments*** of the pending claims that show the claims are enabled. These data rebut any doubts raised by the cited art.. A protein is able to be delivered to both a macrophage and a lymphnode. Thus, the present invention is clearly able to deliver DNA to macrophage cells and is able to express it at adequate levels such that the protein is detectable using routine methods.

Here, Applicants have demonstrated the delivery of a protein to a lymph node, to a macrophage cell, to or to an individual thereby providing working examples and demonstrating that the present invention is enabled (see, for example, pages 29, 33, and 38). Applicants have provided working examples of inducing and/or modulating an immune response (claims 18 and 23) according to the methods of the present invention (see, for example, pp. 30 and 35). Therefore, one of skill in the art would follow the procedures described in Applicants' specification and at most routine experimentation to practice the claimed invention. Without sufficient evidence to dispute the veracity of Applicants disclosure and assertions, the Office ***must*** accept Applicants' disclosure as enabling.

None of the references cited by the Office relate to the invention in the present application. The references have to do with aspects of gene therapy which is thought of as the sustained expression of a nucleic acid sequence in a cell. However, the pending claims are not gene therapy, but rather is for the delivery of a protein. Sustained expression is not a limitation of the claims and should not be read into the claim as the Office appears to be doing when it states that it would be difficult to "express any protein for a long enough period of time." (Office Action, page 14). No period of time is required, rather it is solely the delivery of a protein to the cell or lymphnode as described in the claims, which has been demonstrated in the present application in the Examples (see above).

The Office alleges that macrophages are not easily transduced and thus the pending claims are not enabled and as support cites U.S. Patent Application NO. 2004/0224404. However, the Office appears to be ignoring the evidence within the present application which demonstrates that macrophages are clearly take up and express the nucleic acid molecules of the present invention. As discussed above the Applicants have demonstrated the delivery of a protein to a lymph node, to a macrophage cell, to cells of macrophage derived lineage, or to an individual thereby providing working examples and demonstrating that the present invention is enabled (see, for example, pages 29, 33, and 38). The Office has provided no evidence to rebut these examples to show that they are not enabled. Without such evidence that can show that these working examples are false, the rejection should be withdrawn.

The Office also has raised doubt as to the macrophage specificity of the promoters of p73 and catalase. (Office Action, page 15). The Office has not provided a single reference to doubt the truth of Applicants' assertion that the promoters are macrophage specific. The only thing that the Office has done is state that it could not find "any art that teaches or suggests that such genes are specifically expressed in macrophages." (Office Action, page 15). The Office is reminded that without evidence to the contrary that would suggest the Applicants' specification is incorrect the Office must accept the specification as correct. Accordingly, these promoters are macrophage specific and thus

are enabled as such. If the Office maintains the rejection as directed to these promoter, Applicants request an affidavit by the Examiner stating that these promoters are not macrophage specific.

Accordingly, the Office's inability to provide any ***reasonable evidence*** that would cause one of skill in the art to doubt the truth of the examples in the present specification, the claimed methods are clearly enabled.

Rejections under 35 U.S.C. § 102

Claims 1-2, 29, and 32 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Application No. 20004/0063652.

Claims 1 and 29 have been canceled and the rejection is moot as applied to those claims.

Claims 2 and 32 have been amended to be dependent on claim 5 which recites specific promoters not disclosed in U.S. Patent Application No. 20004/0063652.

Applicants respectfully urge that the rejection of claims 1-2, 29, and 32 under 35 U.S.C. § 102(e) has been obviated.

Rejections under 35 U.S.C. § 103

Claims 5, 7-8, 17, and 22 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent Application No. 20004/0063652 and Kotaoka et al (1997) J. Biol. Chem, 272 (29):18209-15.

Claim 6 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent Application No. 20004/0063652 and Kotaoka et al (1997) J. Biol. Chem, 272 (29):18209-15 and further in view of U.S. Patent No. 5,763,416.

Claim 5 has been amended to delete reference to CD156. Accordingly, the rejections as applied to claims 5-8 and 17 are moot.

Applicants respectfully suggest that the rejection of claim 22 under 35 U.S.C. § 103(a) is an error.

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Applicants respectfully urge that the rejection of claims 5-8 and 17 under 35 U.S.C. § 103(a) has been obviated and that the rejection of claim 22 under 35 U.S.C. § 103(a) is without merit.

Other Matters

The Office has also indicated that if rejections in the present office action are overcome, other rejections might be made based upon U.S. Patent Application No. 2004/0063652. Since the rejection has not been fully explained or described Applicants are unable to respond to a future rejection which has not yet been made. The Office is respectfully reminded that all rejections should be made and that examination is not to be done in a piecemeal manner. If such a new ground of rejection is include in a future office action, that office action should not be final.

Conclusion

Claims 2, 5-10, 12-25, 27-30, 32 and 34-39 are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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